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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,472	01/05/2006	Katia L Hvala	B45323	1605

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
08/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,472	HVALA ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's response to the Office Action mailed 1/12/07 is acknowledged (paper filed 6/12/07). In the amendment filed therein the specification and claims 1, 4, & 5 were modified. Applicant has cancelled claims 2 and 6-9. Currently claims 1 and 3-5 are pending and under consideration.

2. Rejections and/or objections of record not reiterated herein have been withdrawn.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered. See references cited in the specification.

4. The information disclosure statement filed 6/12/07 has been considered as to the merits prior to Final Action.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claim 1 and dependent claims 3-4 are/remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "fragment thereof " in claim 1 is relative term, which renders the claim indefinite. The term "fragment" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to what if any fragments would maintain the activity of the antibody or sequence set forth in claims. Accordingly the claim is not clear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 1 and dependent claims 3-4 are/remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an assay method for binding the hepatitis B surface antigen to anti-HBs rabbit polyclonal antiserum, it does not reasonably provide enablement for any and all immunoglobulins or fragments thereof binding any and all antigens. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure does not set forth any fragments capable of meeting the claimed method and the only antigen exemplified is the hepatitis B surface antigen.

The skilled artisan cannot envision the detailed structure of the encompassed fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

No disclosure, beyond the mere mention of hepatitis B surface antigen and the anti-HBs rabbit polyclonal antiserum is made in the specification. This is insufficient to support the claims drawn to the fragments thereof and the practice of the invention would cause undue experimentation.

Response to Arguments

Applicants contend that immunoglobulin fragments capable of specific antigen binding are well-known in the art, and include Fv, Fab fragments, $F(Ab')_2$ fragments, single chain antibodies, and the like. Therefore, it would be readily apparent to any one of ordinary skill in the art to use fragments that retain the ability to specifically bind the antigen. This argument was carefully considered but not found persuasive because the epitope required for specific binding recognition of the antigen is not taught by the instant disclosure. Accordingly the experimentation required to produce fragments and figure out which ones would retain antigen specificity is deemed undue. The specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. In re Gardner, 166 USPQ 138 CCPA 1970. The rejections are maintained.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claim 1 is/remains rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380).

Yamamoto et al. teach a method of detecting the hepatitis B surface antigen (HB surface antigen or HBsAg). This antigen was produced from aluminium hydroxide adjuvanted hepatitis B (HB) vaccines. See abstract and page 375. The HBsAg was desorbed from alum-gels and quantified. In the method a sandwich enzyme-linked immunosorbent assay (ELISA) is utilized. Specifically the adsorbed HBsAg is mixed with a solution of 0.4M sodium phosphate dibasic and 0.45M sodium citrate at pH 8.5. (Applicants basic buffer) The samples are then diluted with 0.5% casein-PBST (blocking agent). The specification teaches that PBS can be used as a blocking agent in the instant invention on page 5 – 3rd paragraph.

The mixtures were contacted with antibody plates (solid phase) coated with anti-HBs guinea pig polyclonal antibody (immobilized immunoglobulin) and incubated over night. An appropriate dilution of anti-HBs/a mAb was added and detected against controls and standards. See page 375 2nd column.

Response to Arguments

Applicant contends that Yamamoto et al. do not anticipate the instant invention because the HBsAg of adsorbed vaccine was desorbed from alum-gels, then quantitated.

This argument was carefully considered but not found persuasive because the instant claims do not require the measurement of only a complexed antigen-aluminium hydroxide material. Claim 1 step (i) merely recites contacting the *antigen* with an immunoglobulin. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The preamble recites that the antigen being in combination with aluminium hydroxide but the method of claim 1 employs an open transition phrase "comprising" which allows for addition steps (i.e. antigen separation before analysis). Further, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

In addition, the teachings of Yamamoto et al. disclose the quantification of adsorbed HBsAg (antigen in combination with aluminium hydroxide) on page 375 1st column 4th paragraph and 2nd column – middle of the 3rd paragraph.

Applicant also contends that Yamamoto et al. do not anticipate the instant invention because they do not teach the addition of a blocking buffer after the antigen has been contacted with an immunoglobulin. This argument was carefully considered but not found persuasive because Yamamoto et al. disclose the addition of an appropriate dilution of anti-HBs/1 mAb (blocking agent) after the complex formed between HBsAg (antigen) and anti-HBs pAb.

The bound mAb were detected with HRP-conjugated anti-mouse IgG. See page 375 2nd column – Desorption of HBsAg. The specification discloses that the blocking agent is any suitable agent that minimizes non-specific interactions between the antibody-antigen complex and any detection system used to detect the complex. (See page 5 – 3rd paragraph, Antigen).

Applicant argues that Yamamoto et al. do not teach a basic buffer with a ph between pH 8 and pH 10. This argument was carefully considered but not found persuasive because Yamamoto et al. utilize a mixed solution of 0.4M sodium phosphate dibasic and 0.45M sodium citrate (pH 8.5). See page 375 2nd column – Desorption of HBsAg.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

II. Claim 3 is/remains rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380) in view of Katz et al. (Journal of Virological Methods, Vol.25, 1989, pages 101-108).

Please see Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380) as set forth above.

Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380) differ from the instant invention in not specifically teaching assay procedures that are carried out with agitation.

However, Katz et al. teach a method of measuring viral antigens in aluminium hydroxide (AH) adjuvanted vaccines. See abstract. In the ELISA procedure the appropriate antiserum was diluted in 0.05M sodium carbonate buffer at pH 9.6 (basic buffer) and incubated overnight. The wells were then blocked with NFDM in PBS (blocking agent). The samples (commercial vaccines, unadjuvanted viral references, simulated vaccines, and controls) were added and agitated for 2 hours. After washing the plates were detected with a biotinylated anti-mouse IgG antibody, avidin-biotin-alkaline phosphatase conjugate, and *p*-nitrophenyl phosphate. See page 103- ELISA technique.

This procedure is taught to be an improvement over previous *in vitro* antigen quantitation methods because it may be used with intact vaccines but does not have the problems associated with the use of isotopes. It offers the convenience of ELISA without requiring antigen-AH dissociation and separation prior to measurement. See page 107 2nd paragraph. The method can be applied to AH adjuvanted vaccines as a class. Further, the method may minimize biological variability, time, expense, and humane difficulties associated with in vivo vaccine potency analysis. See page 107 last paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ the agitation method of Katz et al. in the hepatitis B surface antigen detection of Yamamoto et al. because Katz et al. taught that his procedure was an improvement over previous *in vitro* antigen quantitation methods because it may be used with intact vaccines but does not have the problems associated with the use of isotopes. It offers the convenience of ELISA without requiring antigen-AH dissociation and separation prior to measurement. See page 107 2nd paragraph.

One of ordinary skill in the art would have been motivated the employ the method of Katz et al. because it can be applied to AH adjuvanted vaccines as a class. Further, the method may minimize biological variability, time, expense, and humane difficulties associated with in vivo vaccine potency analysis. See page 107 last paragraph.

Response to Arguments

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant contends that Katz et al. do not teach blocking after the antigen is brought into contact with the immunoglobulin or a buffer at pH between 8 and 10. This argument was carefully considered but not found persuasive because Yamamoto et al teach the limitations. Specifically, Yamamoto et al. disclose the addition of an appropriate dilution of anti-HBs/1 mAb (blocking agent) after the complex formed between HBsAg (antigen) and anti-HBs pAb. The

bound mAb were detected with HRP-conjugated anti-mouse IgG. See page 375 2nd column – Desorption of HBsAg. The specification discloses that the blocking agent is any suitable agent that minimizes non-specific interactions between the antibody-antigen complex and any detection system used to detect the complex. (See page 5 – 3rd paragraph, Antigen). Further, Yamamoto et al. utilize a mixed solution of 0.4M sodium phosphate dibasic and 0.45M sodium citrate (pH 8.5). See page 375 2nd column – Desorption of HBsAg.

Katz was merely added to teach assay procedures that are carried out with agitation.

While a deficiency in a reference may overcome a rejection under 35 USC 103, a reference is not overcome by pointing out that a reference lacks a teaching for which other references are relied. In re Lyons, 364 F.2d 1005, 150 USPQ 741, 746 CCPA 1966.

III. Claims 4 and 5 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380) in view Kono et al. (JP 11201970 – Abstract Only).

Please see Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380) as set forth above.

Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380) differ from the instant invention in not teaching the use of BSA in their procedure.

However, Kono et al. teach a method for measuring hepatitis B surface antigens or antibodies with sensitized latex particles. In the procedure the immobilized reagents are treated with blocking agent and incubated with a non-immunoreactive protein and/or hydrolysis product to reduce background (non-specific binding) and largely increase specific signal for the immunoassay. The particles were treated with BSA, in the specific embodiment of the abstract.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to employ BSA as exemplified by Kono et al. in the method of Yamamoto et al. (Biologicals, 1997, Vol.25, pages 373-380) because Kono et al. taught that in such procedures where the immobilized reagents are treated with [BSA] blocking agent and incubated with a non-immunoreactive protein and/or hydrolysis product it reduces background (non-specific binding) and largely increase specific signal for the immunoassay. See Kono et al. abstract.

Although Kono et al. disclose BSA the abstract is silent regarding the concentration. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the optimal working concentration of BSA, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272,205 USPQ 215 (CCPA 1980).

Response to Arguments

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant contends that Kono et al. do not teach blocking after the antigen is brought into contact with the immunoglobulin or a buffer at pH between 8 and 10. This argument was carefully considered but not found persuasive because Yamamoto et al teach the limitations. Specifically, Yamamoto et al. disclose the addition of an appropriate dilution of anti-HBs/1 mAb (blocking agent) after the complex formed between HBsAg (antigen) and anti-HBs pAb.

The bound mAb were detected with HRP-conjugated anti-mouse IgG. See page 375 2nd column – Desorption of HBsAg. The specification discloses that the blocking agent is any suitable agent that minimizes non-specific interactions between the antibody-antigen complex and any detection system used to detect the complex. (See page 5 – 3rd paragraph, Antigen). Further, Yamamoto et al. utilize a mixed solution of 0.4M sodium phosphate dibasic and 0.45M sodium citrate (pH 8.5). See page 375 2nd column – Desorption of HBsAg.

Kono et al. were merely added to teach the use of BSA.

While a deficiency in a reference may overcome a rejection under 35 USC 103, a reference is not overcome by pointing out that a reference lacks a teaching for which other references are relied. In re Lyons, 364 F.2d 1005, 150 USPQ 741, 746 CCPA 1966.

9. For reasons aforementioned, no claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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